REMARKS

The applicants note with appreciation the examiner's allowance of claim 11 and agreement that claim 4 contains allowable subject matter.

The applicants further thank the examiner for looking at a draft of this response and providing some comments thereon. The response as filed recognizes these comments and includes some further changes requested by the applicant, but it is not believed that these should raise any additional issues of patentability.

Claim 1 has been limiting the definition of X^1 to ArX wherein X is defined as a subset of the original X^3T definition based on the original exemplification as set out below:

R1	R2	R3	X	compound
Me	Me	Me	N, N-dimethylamino-; -N(Me) $_2$	10c
Me	Me	Me	N-methylamino-; -NH(Me)	10d
Me	Me	Me	N-methyl-N-(3-methoxypropyl)amino-; -N(Me)(CH_2 CH_2 CH_2OCH_3)	page 34 line 21
H	Me	H	N,N-di-(2-hydroxyethyl)-amino-; -N(CH_2 CH_2OH)$_2$	page 34 line 26
H	Me	H	2-hydroxyethylamino-; -NH(CH_2 CH_2OH)	page 34 line 27
H	Me	H	2-methanesulfonatoethylamino)-; -NH (CH_2 CH_2OSO_2 CH_3)	page 35 line 5
H	Me	H	2-(N,N-diethylamino)ethylamino]-; -NH (CH_2 CH_2) N(CH_2 CH_3)$_2$	page 35 line17
Me	Me	Me	4'-(methylsulfonamido)-; -NH(SO_2CH_3)	10e
CH_2OCH_2		H	4'-[2-(N,N-diethylamino)ethoxy]-; -OCH_2 CH_2 N (CH_2 CH_3)$_2$	page 35 line 31
Me	Me	Me	2,3-dihydroxy-propyloxy-; -OCH_2 CH (OH) CH_2OH	page 36 line5
Me	Me	Me	4'-(Carbmethoxymethoxy)-; - OCH_2 CO_2 CH_3	12a
Me	Me	Me	4'-methoxy	1c
H	H	H	4'-hydroxy	1d
Me	H	H	4'-hydroxy	1f
Me	H	H	4'-methoxy	1g
Me	Me	Me	4'-hydroxy	1h
Me	Me	Me	4"-nitro	8
Me	Me	H	4'-nitro	9a
H	Me	H	4'-nitro	9b
Me	Me	Me	4'-NH_2	10a
H	Me	H	4'-NH_2	10b
H	sulfate		H H	11a

H	phosphate	H	H	11b
Me	carbethoxymethoxy	H	4'-methoxy	page 34 line 10
Me	Me	Me	4'-carbethoxymethoxy $OC_2H_4CO_2CH_2$	page 34 line 16
CH_2OCH_2		OH	4'-[2-(N,N-diethylamino)ethoxy $OCH_2CH_2N(CH_2CH_3)_2$	page 35 line 32

Method claims 14, 18, 31, 46, 54 and 60 have all been amended to replace reference to "treatment" to the specific aspects of treatment that the examiner accepts are enabled, namely improvement in the condition of a patient and delay in progression of the disease. Support for these effects is found at the bottom of page 12 and the top of page 13 of the specification.

New claim 61 parallels claim 12 but is dependent on claim 11.

It is believed that the Rejection under 35 USC 112 paragraph 1 claims has been overcome by the amendments set out above.

Turning now to the issues raised under 35 USC 112 paragraph 2, the definition of X1 has been amended to meet the rejection.

Claim 31 has been amended to show X as the definition of the substituent in formula V and following a telephone conversation with the Examiner following submission of a draft of this response has been further limited to define the conditions to be treated to liver, kidney and lung damage.

Turning now to the rejection under 35 USC 102 of claims 31 and 45, Claim 31 has been amended to delete the possibility that X may be hydrogen so that oroxylin A no longer falls within the definition of the specified compounds. As noted above, claim 31 has also been amended to define the conditions being treated more precisely. Lee states that his compounds are of use to for inhibiting iNOS, inhibiting COX-2, activating K+ channels, treating septic shock, preventing aneurysms, inhibiting expression of angiotensin converting enzyme and reducing inflammation. There is no mention of effecting any type of treatment of organ damage.

This therefore leaves the rejection of claims 1, 12, 14, 18, 31, 39, 44 53 and 60 under 35 USC 103 over Lee WO 01/30342.

The relevance of Lee has been discussed previously, for example in the telephone interview of Feb. 25, 2010. Having regard to claim 1, it is pointed out that this has now been amended to limit the definition of R^2 to H, lower alkyl, $-SO_3H$ or PO_3H and X^1 to be substituted phenyl which are based on claim 11. Lee contains no suggestion that X other than H should be present in his compounds in any position of X^1=ArX or the B ring of flavone. Nor is there any reason why one skilled in the art would have thought to modify Lee's compounds to introduce either of these groups (X) in the B ring. It is therefore submitted that claims 1 and claim 12 meet the requirements of 35 USC 103.

Turning now to the method of treatment claims, it is submitted that Claim 18 which defines the active compounds in the same terms as claim 1 is not obvious over Lee for the same reasons that claim 1 itself is not obvious over Lee who teaches nothing about liver, lung and kidney damage nor any one skilled in the art would be able to be so creative to extend what Lee demonstrated in the *in vitro* assays to these novel utilities.

This then leaves Claim 31, and the claims dependent on it, Claim 46 and claim 60.
It is the applicant's position that Lee does not provide an enabling disclosure that would point one of ordinary skill in the art towards the present invention as now claimed. Lee did not do any experiments on TNF or superoxide. The latter is not mentioned in his patent al all. Lee et al did not demonstrate that their compounds is effective in treating sepsis, either at cardiovascular crisis or at mortality (ie after organ failure). Applicants submit that Lee's patent teaches any thing relevant to their invention. Lee does not teach anything about treatment of organ damage at all. Even for the conditions they do mention, they did not do any experiments in TNF α nor superoxide anion radicals. Besides, they did not have any in vivo data to validate their in vitro data in the area of iNOS, K-channel and cyclooxygenase. Applicants have been involved in drug R&D for more than 20 years and would share the same view as those skilled in the art that most of in vitro data have difficulty in getting validated in vivo, a part of barrier in the translational research. The in vitro data presented by the applicants in the present application is consistent their findings in vivo. Besides, the

claimed treatment has been validated in clinical trials, as discussed in the previous responses as in our application.

The Examiner refers to pages 14 – 16 of Lee. The Applicants could not find any wordings related to TNF neither superoxide anion radical on pages of 14-16 of WO 01/30342 A1. Oroxylin is 4'-unsubstitued bacailein analog. The present invention is concentrated on novel 4'-substitued 5,6,7-trihydroxychromones which is different from Fig 1B in two respects:

1) utility: Fig 1B demonstrated in vitro activities in iNOS, potassium channel and cyclooxygenase activities, while we demonstrated anti-TNF activity in vitro and in vivo and anti-LPS activities in vivo.
2) Our compounds are new compounds, substituted aniline or phenolic derivatives, while oroxylin is a benzene derivative (unsubstituted B ring).

Additionally it should be noted that Claims18, 31, 44 and 60 are limited to improving the condition of or delaying in progression of liver damage, lung damage or kidney damage. Lee makes no mention whatsoever of any such effect nor is there anything in Lee that would point to such an effect.

Furthermore, nothing in Lee points to the use of compounds having the combination of 6-substituent and X^1 or X is as now defined in any of the claims for any purpose. In particular Lee has no disclosure of compounds wherein the 6 position is substituted by a sulfate or phosphate as required by claim 46.

In view of the foregoing, it is submitted that this application is now in order for allowance.

Respectfully submitted,

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